

Artificial Neural Network based Classification of Neurodegenerative Diseases

ANN Classifies Neurodegeneration

Nivedita Chaudhary^{*1}, Yogender Aggarwal², Rakesh Kumar Sinha³

Center for Biomedical Instrumentation, Birla Institute of Technology, Mesra, Ranchi-835215 Jharkhand, India

^{*}sunshinenive@gmail.com; ²yogender.aggarwal@gmail.com; ³rksinhares@gmail.com

Abstract

Neurodegenerative disease occurs due to deterioration of cells specially the myelin sheath of the neurons; of brain, spinal cord, and peripheral nerves. The economic and social burden of neurodegenerative diseases is massive and rising too rapidly. Among several of different neurodegenerative disorders, present work is focused on the three most common; Alzheimer's disease, Parkinson's disease, and Huntington's disease. Although the most consistent risk factor for developing a neurodegenerative disorders is increasing age, it has been observed that the symptoms of all the three diseases overlap with each other, clinically and pathologically. Therefore, their practical classification is quite challenging and thus needing an automated tool to classify them. In the present model, backpropagation artificial neural network (ANN) has been designed to classify neurodegenerative disorders according to their symptoms. The 27:70:3 architecture of ANN has been used to predict the clinical outcome from the complex overlapped symptoms that are routinely available to clinicians. The model has found to be effective in differentiating the different types of focused diseases with an overall performance of 96.42%.

Keywords

Artificial Neural Network; Automated classification; Neurodegenerative diseases

Introduction

Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expression affecting specific subsets of neurons in definite functional anatomic systems: they arise for unknown reasons and progress in a relentless manner (Przedborski et al., 2003). The autosomal-dominant neurodegenerative diseases are fallen into two categories, the polyglutamine diseases and the tau- and synucleinopathies (Hardy & Gwinn-Hard, 1998). They are also crudely divided into two groups according to phenotypic effects; ataxia, condition causing problems with movements and dementia, condition affecting memory. There are three common

forms of neurodegenerative disorders; Alzheimer's Disease (AD), Parkinson's Diseases (PD) and Huntington's Disease (HD). Where AD is related

to dementia, PD is related to ataxia and HD having symptoms of both ataxia and dementia. AD is one of the most common neurodegenerative disorders, and it is the fourth leading cause of death following cardiovascular diseases, cancer and stroke (Hu et al., 2004). Basically, it is a progressive and devastating age related disorder that is the primary cause of dementia in subjects over the age of 65 years (Seshadri et al., 1997), which is characterized by progressive memory loss (Bryan et al., 2008) impairments in behavior, language and visual-spatial skills and ultimately leading to death (Webber et al., 2006). PD is the second most common neurodegenerative disease occurred among elderly people (Takahashi & Imai, 2003). It is a chronic, progressive neurodegenerative disorder that affects at least 1% of people by age 70 (Savitt et al., 2006). Regarded as the loss of dopamine-containing neurons in the substantia nigra pars compacta (Brochard et al., 2009). Clinically described by the symptoms of bradykinesia, resting tremor, rigidity, postural instability, autonomic, cognitive and psychiatric disturbances (Moore et al., 2005). HD is a debilitating neurodegenerative disorder caused by an abnormal allele on chromosome four (Eskenazi et al., 2007). The mean age at onset is 40 years (Witjes-Ane et al., 2003), symptoms usually consisting of uncontrolled movements, emotional disturbances, mental deterioration, Psychiatric abnormalities, including depression, anxiety, apathy, and irritability, cognitive deficits or dementia as well as weight loss, choreic movements, and other motor deficits including dystonia and rigidity (Li & Li, 2006). It is fatal and causes death within 15-20 years from the onset of the symptoms (Wu et al., 2008). But these diseases are not well understood at the molecular level, which is almost impossible to diagnose these diseases at its early stage

because it begins long before the patient experiences any symptoms. These symptoms have been overlapped at their early stage causing difficulties in the symptomatic classification of these diseases.

A single symptom or a set of symptoms may be indicative of all three conditions, thus the automated classification of neurodegenerative disease is important because manual screening is a tedious and error-prone task. ANN models are based on a set of multilayered interconnected equations which use non-linear statistical analysis to reveal previously unrecognized relations between given input variables and an output variable. Several studies have shown that ANN is accurate and reliable in diagnosis and outcome prediction in diverse clinical setups (Sinha, 2008). Its methodology appears promising for studying neurodegenerative disorders (Litvan et al., 1996). Thus, the present work has been aimed to develop an ANN model to predict the clinical outcome, by means of symptoms routinely available to clinicians, in a group of patients presenting with AD, PD and HD.

Study Design Framework

Data Collection

The clinical symptoms of neurodegenerative disorders have been studied with the help of an expert clinician and are identified as six major classes: (a) Memory problems, (b) Communication problems, (c) Personality changes, (d) Idiosyncratic behaviors, (e) Loss of voluntary control and (f) Common health problems. The characteristics of the three neurodegenerative diseases (AD, PD & HD) under each of the mentioned major classes are further focused on the specific symptoms and explained in TABLE 1a-f. Appearance of majority of these clinical symptoms, if not all, is used as confirmatory parameters in clinical domain for these diseases.

Study Design

The present paper has used three-layered feed-forward backpropagation ANN to classify different stages of neurodegenerative diseases (AD, PD and HD) patients based on clinical symptoms (TABLE 1a-f). The digital values of clinical AD, PD and HD symptoms between 0-1 have been used to build the predictive model.

The ANN network was coded using C++ programming language on a computer (Rao & Rao, 1996). The network was trained for one million iterations with the error tolerance level and learning rate parameters were

assigned 0.01 and 0.1, respectively. The backpropagation neural network takes advantage of available effective training and better-understood system behavior. Neurons or nodes in each layer are interconnected in a feed-forward fashion. The connections between different layers of nodes have associated weights which act upon outputs of the first layer of nodes before they are processed next. The hidden nodes and output layers have a transfer function. The sigmoid function was used in this study (Aggarwal et al., 2007). The weights were adjusted as follows:

$$W_{ij}(t+1) = W_{ij}(t) + \eta \delta_j X_i + \alpha (W_{ij}(t) - W_{ij}(t-1)) \quad \text{Eq.1}$$

Where $W_{ij}(t)$ is the connection weight from a node i in one layer at time t , X_i is either an input or the output of the hidden node i , δ_j is an error term for node j , η is a learning rate factor and α is a momentum factor ($0 < \alpha < 1$). If j is an output node, then

$$\delta_j = y_j(1 - y_j)(d_j - y_j) \quad \text{Eq.2}$$

Where, d_j is the desired output of node j and y_j is the actual output. If node j is a hidden node, however, the computation of error terms becomes

$$\delta_j = X_j(1 - X_j) \sum_k \delta_k W_{jk} \quad \text{Eq.3}$$

Where k is summed over all nodes in the layer above node j . Hidden node thresholds were adjusted in a similar way by assuming they are connection weights on links from auxiliary constant-valued inputs.

The ANN used in the present study has 27 nodes in the input layer, 70 nodes in the hidden layer and 3 nodes in the output layer. The criteria of classification of all three disorders have been presented in TABLE 2. The first output represents normal condition (000), second output represents representing AD-mild (100), third AD-moderate (010), fourth one AD-severe (001), fifth output represents PD primary symptoms (011), sixth PD secondary symptoms (110) and last output Huntington's (101).

Estimation of the Diseases

In the three-layered ANN configuration, digital values of the clinical neurodegenerative disease symptoms were used as the input vector to the ANN. The 27:70:3

TABLE 1 CLINICAL VARIABLE USED TO BUILD THE PREDICTIVE MODEL

1 a: MEMORY PROBLEMS

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Confusion	Confusion starts occurring	Dose not recognizes self in the mirror, may think that a television story in real				Decreased concentration
Absentmindedness	Forgets names and word, forgets their own history, recent personal events and current events	Forgets recent events. Forgets their own history, no longer remembers their own address or phone	Doesn't recognize familiar people, including their spouse and family members			Forgetfulness and memory decline, difficulties in remembering facts
Ability of thinking	Less able to plan, organize, or think logically, withdraws from social and mental challenges	Can no longer think logically or clearly				
Arithmetic problems	Money and math problems	Arithmetic and money problems escalate				
Disorientation	Disorientation in time and place	Disorientated about the season, the time of day				

1 b: COMMUNICATION PROBLEMS

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Conversation	May converse normally until a memory lapse occurs	Problems with speaking understanding reading, and writing, may revert to their first speaking language (and need a multilingual caregiver)	Either doesn't speak or speaks incoherently		Soft whispery voice	Slurred speech
Comprehension	Increasing difficulties comprehending reading materials	May still be able to read, but cannot respond correctly, problems finishing sentences	Can't write or comprehend reading material		Small cramped handwriting	Difficulty in learning new things
Reiterate		Repeats stories words, and gestures; repetitive questions				
Slow response	Begins to have difficulty in expressing themselves				Slow response to questions	Difficulty in making decisions or answering questions
Poor judgments						Poor judgment, difficulty in driving

1 c: PERSONALITY CHANGES

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Illusion		May accuse spouse of having an affair, or accuse family members of stealing delusional, has illusion, may hear, see, smell, or taste things that aren't present				Delusion, hallucinations
Depression		May have an exaggerations of their normal personality characteristics	Dulling of the personality		depression	Bipolar disorders (manic-depression)
Mental disorders	Apathetic, withdraw, avoids people anxious, irritable	Apathetic, withdraw anxious, agitated unmannerly, aggressive or threatening suspicious, paranoid	Apathetic, withdrawn (continues from early stage Alzheimer's)		Anxiety, isolation	Hostility, irritability, apathy, mood swing, irritability, progressive mental deterioration
Emotional changes	Insensitive to others feelings, easily angered when frustrated, tired, rushed, or surprised		Appears uncomfortable but cries out when touched or moved, can no longer smile, groan or mumble loudly			Unprovoked aggression, paranoia, lack of pleasure and joy, disinterest in life

1 d: IDIOSYNCRATIC BEHAVIORS

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Repetitive movements	Forgets to eat, or eats constantly or eats only one kind of food	Restlessness, pacing, repetitive movements fingers certain objects over and over again, tries doorknobs, hand wringing, tissue shredding	May pat touch thing repeatedly			
Wandering	Hoards, checks, or searches for objects of little value	Wandering including chatting to oneself while wandering, rummages through things, hides things	No more wandering			
Disruption of the normal sleep wake cycle		Disruption of the normal sleep-wake cycle "sun downing"				

1e: LOSS OF VOLUNTARY CONTROL

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Bradykinesia		Increases overtime has trouble getting comfortable in a chair or on the toilet, muscle twitches	Cannot control their movements	Slowness in voluntary movements such as standing up, walking and sitting down, freezing episodes		Increased clumsiness, continual muscular contractions
Tremors				Often occur in the hands, fingers, forearms, foot, mouth or chin		Development of tics (involuntary movements) in the fingers, feet, face or trunk, agitation
Rigidity			Muscles are rigid	Stiff muscles, muscles pain during movement		Muscle rigidity, neck muscle rigidity
Poor balance			Cannot walk, stand, sit up or hold up their head without assistance	Unsteady balance which oftentimes leads to fall, loss of reflexes that help posture		Loss of coordination and balance, stumbling or falling, unsteady walking, gait problems

1 f: COMMON HEALTH PROBLEMS

Stages	AD			PD		HD
	Early stage (mild)	Mild stage (moderate)	Late stage (severe)	Primary symptoms	Secondary symptoms	
Loss of bowel and bladder control		Health starts declining, urinary and fecal incontinence	Complete urinary and bowel incontinence		Constipation, loss of bowel and bladder control	
Throat, mouth and oesophagus complications			Cant swallow, may choke		Difficulties in swallowing, choking, coughing or drooling, excessive salivation	Jaw clenching or teeth grinding, difficulty swallowing or eating
Dermatologic al effects					Excessive sweating, scaling, dry skin on the face or scalp	
Dependence			Need complete help with all activities of daily living, requires full-time care, bedridden		At advanced stage needs complete assistance	
Body shuts down			Body shuts down, brain cannot interpret the input			Lack of energy
Spasm/ impairment	SpasM/ impairment					Finger, toe, facial, muscle, limbs, trunk and chorea spasm, motor, cognitive and emotional impairment

architecture of ANN was obtained with the optimization for both training and testing purpose. During training, a training file 'TRAINING.DAT' with the digital values of all three diseases symptoms along with an output was presented to the input. The error tolerance, number of iterations and learning rate parameter were assigned as 0.01, one million and 0.1, respectively. Once the simulator reaches the error tolerance specified or achieved the maximum number of iterations, assigned for training, the simulator saves the state of network by saving all its weights in 'WEIGHT.DAT' file. The output values have been compared to the desired outputs and if the outputs have been found to be the same as desired outputs, no further training is required. Otherwise weights have to adapt further by training with least mean square rule. Obtaining the error in minimum possible value results in absolute correction. During testing, the testing file 'TEST.DAT' with digital values of clinical symptoms is presented to the input nodes of ANN, which reads the input and finds the output of the network.

TABLE 2: CLASSIFICATION CRITERIA WITH THE PRESENT ANN MODEL

Output states			
Diseased condition	First output neuron	Second output neuron	Third output neuron
Alzheimer's (mild)	1	0	0
Alzheimer's (moderate)	0	1	0
Alzheimer's (severe)	0	0	1
Parkinson's (primary symptoms)	0	1	1
Parkinson's (secondary symptoms)	1	1	0
Huntington's disease	1	0	1
Normal condition	0	0	0

Testing Protocols

Our sample size consist of 160 data sets (20 training sets and 140 test sets) described by seven different classes (mild AD, moderate AD, severe AD, primary PD, secondary PD, HD, and normal) and 3 neurons in output layer with 70 neurons in the hidden layer.

Result and Discussion

Before applying the ANN for the classification of all three diseased conditions, the network needs to be optimized to get optimum performance. Different learning rates were investigated in the range of 0.1-0.5.

The best performance was obtained for testing set when the learning rate was chosen as 0.1 with which an overall accuracy of 96.42%. The effects of number of hidden nodes in the range of 10-90 with a fixed number of iterations (1 million) are tested. 70 hidden nodes resulted in the best performance compared with other combinations of hidden nodes (TABLE 3). With the 27:70:3 structure and optimized learning rate value (0.1), the ANN identified the 140 diseased condition test sets with an accuracy of 96.42%.

TABLE 3: EFFECT OF LEARNING RATE AND NUMBER OF HIDDEN LAYER NODES ON THE PERFORMANCE OF ANN AT FIX ERROR TOLERANCE 0.01 (TESTING RESULTS)

Hidden layers	Learning rate parameter		
	0.1	0.2	0.3
10	67.14	28.57	27.41
20	90.00	87.65	00.00
30	92.85	88.57	95.71
40	90.00	87.85	94.28
50	90.71	90.00	92.14
60	93.57	88.57	95.00
70	96.42	95.00	88.57
80	86.42	88.57	91.40
90	90.00	89.28	84.28

ANN is being applied to broad areas of prediction and classification. In the field of health and medicine, it is used by many researchers for diagnosis and prediction of diseases. Neural networks are powerful computational methods that have resulted from work in the area of neurophysiology and are being applied to an increasing range of medical problems (Paliwal & Kumar, 2009). In some previous works, ANN was used to predict cause-specific death from colorectal cancer for individual patients that provided by clinical judgment (Bottaci et al., 1997). ANN was also found comparatively the most efficient in the classification of non-periodic and nonlinear types of signals (Sinha, 2008). The potential of ANN has been investigated in diagnosing thyroid diseases (Zhang & Berardi, 1998). ANN along with logistic regression is applied to diagnose Methicillin-Resistant Staphylococcus Aureus (Shang et al., 2003). It is also used in classification of heart sounds for its discriminative training ability and easy implementation (Ari & Saha, 2009). In the field of neurodegenerative diseases, ANN is applied for classification of cognitively normal, demented, AD and vascular dementia from single photon emission with computed tomography image data from brain

(deFigueiredo et al., 1995), to distinguish AD patients from controls in the nun study (Grossi et al., 2007), also for the classification of essential tremor, PD tremor, and physiological tremor (Ai & Wang, 2008). In 1996, Litvan et al. (1996) applied supervised and unsupervised ANN for differentiating the subtypes of progressive supranuclear palsy (PSP), and in differentiating PSP from postencephalitic parkinsonism (PEP) and corticobasal degeneration, or Pick's disease from corticobasal degeneration. Input data for each case consisted of values representing histological features, including neurofibrillary tangles, neuronal loss and gliosis found in multiple brain sampling areas. The supervised learning ANN achieved excellent accuracy in classifying PSP but it had difficulty in classifying the other disorders.

There have been no reports on the application of ANN methods for symptomatic diagnostic classifications of neurodegenerative disorders with the help of symptoms regularly available to the clinicians. There are no clinically useful predictive techniques available to aid the physician in the diagnosis of patients. In this study, we attempted to employ ANN based modelling techniques to envisage the severity of all three diseased conditions, AD (mild, moderate, and severe), PD (primary symptoms and secondary symptoms) and HD. For any predictive technique to be useful in making a diagnostic decision, an important feature is that only data that are readily available to the clinician at the time of diagnosis are used. Our model used only data derived from clinical history and physical examination. We accentuate that our model is not meant to replace or substitute for an experienced clinician; on the contrary, we suggest that the model should be viewed as a decision aid for the busy clinicians. The result of this study are promising, suggesting that a system based on this approach will be accurate and user friendly, while simple enough to be implemented at low cost. The present report shows overall 96.42% sensitivity in classification of Neurodegenerative disease. Input layer of ANN was designed with 27 most identified clinical data. However, the addition of any new clinical symptom and further training and testing of ANN can alter the recognition pattern. In the current investigation, all 160 data sets of neurodegeneration cases have been recorded and provided by expert clinicians. The outcome of the ANN was also tested clinically for these data sets and it can be presumed that the present architecture 27:70:3 can provide a platform to develop an automated system to support clinicians and

researchers. It has already been established that the success of ANN in classification involves the optimization of the network structure and the parameters. In the present study, various combinations of three-layered back propagation network were tested with assigning different learning rate parameters and the most reliable performance rate was derived with the ANN configuration of 27:70:3. However, potential clinical studies are now needed to assess the ability of ANN model to improve the patient management and healthcare resources in clinical practice and in diverse population.

Conclusions

Neurodegenerative disease holds very multifaceted indicative structural design. Symptoms of one diseased condition overlap with other diseases too. If it is classified on the basis of symptoms perceptible at the very early stage of disease, people could be treated before it becomes worse over time. This work is intended to design an automated classification system for the pathological diagnostic of the disease in its infancy stage. Backpropagation ANN is precise and reliable in diagnosis and outcome prediction in varied clinical setting which will ultimately support Clinicians and Researchers, and patients could be treated for such disease prior to commencement of disease helping millions of people to live their normal life.

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